REMARKS

Claims 1 to 14 and 19 to 23 are currently pending in the application. As discussed below, by the present Response claims 1, 10, and 20-23 have been amended to clarify the subject matter of the claims. Claim 4 is amended to correct the capitalization of cDNA. Claim 19 is amended to correct the spelling of connexin. Claims 15 to 18 have been withdrawn as non-elected subject matter, pending allowance of the linking claims. New claim 24 has been added. No new matter is added.

Applicants' Invention

The Applicants' invention comprises a novel way of delivering an oligonucleotide or a plasmid expressing an oligonucleotide, or a peptide product thereof into a cell, termed a "target cell," by first introducing the oligonucleotide or plasmid into a donor cell, and then contacting the target cell with the donor cell under conditions that permit the donor cell to form a gap junction channel with the target cell. The oligonucleotide, or a plasmid expressing an oligonucleotide, or a peptide product thereof, is thus delivered into the target cell from the donor cell.

The donor cell may be *e.g.*, a mesenchymal stem cell or other cell type capable of forming a gap junction with the target cell. In order to promote the formation of gap junctions, the donor cell may be engineered to express one or more connexin(s). The selected oligonucleotide, plasmid expressing an oligonucleotide, or a peptide product thereof, is delivered into the target cell from the donor cell by traversing the gap junction.

The claims have been amended to specify that the oligonucleotide selected for delivery into the target cell is first introduced into the donor cell "*in vitro*." Further, the claims have been amended to specify that the oligonucleotide is delivered from the donor cell to the target cell "by traversing the gap junction" formed between the donor and target cell. We respectfully submit that the claims as presently amended are in condition for allowance.

Specification

The non-patent literature in paragraph 0035 is provided in an IDS, being filed along with this Response.

Claim Objections

Claim 19 was amended to correct the spelling of connexin.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-14 and 19-23 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. However, it appears that the basis of this rejection lies in a misinterpretation of the claimed method. The claims have been amended as discussed below to clarify the subject matter of the claims. We respectfully submit that the claims as presently amended are in condition for allowance.

The Examiner states that the specification

> does not reasonably provide enablement for an *in vivo* method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel . . .

(Office Action dated September 16, 2008, at page 5, emphasis added). The Examiner concludes that "interpreted broadly, the claims encompass delivering an oligonucleotide to a target cell in a human subject" (Office Action dated September 16, 2008, at page 6).

However, it appears that the Examiner's rejection is based on a misunderstanding of the claims. Rather than introducing an oligonucleotide directly into a target cell in a human subject, the invention provides a method wherein an oligonucleotide or plasmid is first introduced into a donor cell *in vitro*. The Examiner clearly states that this first step is enabled, "while being enabling for an *in vitro* method of delivering an oligonucleotide or plasmid expressing an oligonucleotide into a target cell . . ." (Office Action dated September 16, 2008, at page 5). The next step in the claimed method is to contact the donor cell with a target cell to introduce the oligonucleotide, the plasmid expressing the oligonucleotide, or a peptide product thereof to the target cell via gap junctions.

As evidence for the state of the art of art of antisense delivery, the Office provided three references, Braasch et al. (Biochemistry, 2002 Vol. 41, pp. 4503-10), Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6, pp. 72-81), and Gewirtz et al. (PNAS 1996 Vol. 93, pp. 3161-3). According to the Examiner, each of these articles raises the problems pertaining to the delivery and uptake of oligonucleotides by cells. However, each of these references discuss delivery of oligonucleotides directly to the target cells. The present invention is directed to a novel method for introducing an oligonucleotide, a plasmid expressing the oligonucleotide, or a peptide product thereof into target cells by first introducing the oligonucleotide or plasmid into a donor cell, and second, contacting the donor cell with the target cell so that oligonucleotide, the plasmid expressing the oligonucleotide, or a peptide product thereof, can enter the target cell via gap junction(s) formed with the donor cell. Thus, the present invention provides a novel method for addressing the problems with oligonucleotide delivery raised by the Examiner.

The claims have been amended in order to clarify the claimed method. As amended the claims specify that the oligonucleotide selected for delivery into the target cell is first introduced into the donor cell "*in vitro*." Further, the claims have been amended to specify that the oligonucleotide is delivered from the donor cell to the target cell "by traversing the gap junction" formed between the donor and target cell. Applicants respectfully submit that a person skilled in the art would be able to perform the claimed method without undue experimentation. Thus, Applicants respectfully submit that the pending claims fully comply with the enablement requirement of section 112.

Rejection Under 35 U.S.C. § 102

Claims 1, 3, 4, 8-12, 14, 20, 21, and 23 were rejected under 35 U.S.C. § 102(a) as being allegedly anticipated by Frendo et al. (J. of Cell Science, 2003 Vol. 116, pp. 3413-21). Again it appears these rejections are based on a misunderstanding. Applicants respectfully submit that the claims as amended are in a condition for allowance.

Frendo et al. examined the involvement of Cx43 in trophoblast cell fusion by introducing Cx43 antisense RNA into human villous cytotrophoblasts. Frendo et al. introduced the Cx43 antisense RNA into human villous cytotrophoblasts in order to reduce the expression of Cx43. Frendo et al. do not disclose a method wherein an oligonucleotide or plasmid is first introduced into a donor cell and then, second, the donor cell is used to introduce the oligonucleotide, a plasmid expressing an oligonucleotide, or a peptide product thereof, to the target cell via gap junctions. In fact, by purposefully reducing the

levels of Cx43, which forms gap junctions, Frendo et al. would inhibit this second step from occurring via Cx43 gap junctions.

Further, in Frendo, there is only one population of cells, the cells into which the oligonucleotides are introduced. In the claimed methods, there are two populations of cells, the donor cells, into which the oligonucleotide or plasmid is introduced in step a), and the target cells, into which the oligonucleotide or the plasmid is not introduced in step a), but rather which receives the oligonucleotide only as a consequence of being contacted with the donor cell. The person of ordinary skill in the art would understand this from the wording of the claims, which entail two steps, preparing donor cells and contacting target cells with donor cells in such a way that an oligonucleotide or peptide is delivered from the donor cell to the target cell via gap junctions.

Claims 1, 3, 4, 6, 10-12, 14, 20, 21, and 23 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Li et al. (J. of Cell Biology, 1996 Vol. 134, pp. 1019-30).

Li et al. studied Cx43 hemichannels, which are Cx43 assemblies in the plasma membrane of a cell that have not formed a gap junction with another cell. Li et al. transfected a Cx43 antisense expression vector into Novikoff cells in order reduce the levels of Cx43. Li et al. do not disclose a method wherein the oligonucleotide is first introduced into a donor cell and then, second, the donor cell is used to introduce the oligonucleotide, or a plasmid expressing an oligonucleotide, or a peptide product thereof, to the target cell via gap junctions. In fact, by purposefully reducing the levels of Cx43, which forms gap junctions, Li et al. would inhibit this second step from occurring via Cx43 gap junctions.

Further, in Li, as in Frendo, there is only one population of cells, the cells into which the oligonucleotides are introduced. In the claimed methods, there are two populations of cells, the donor cells, into which the oligonucleotide or plasmid is introduced in step a), and the target cells, into which the oligonucleotide or the plasmid is not introduced in step a), but rather which receives the oligonucleotide only as a consequence of being contacted with the donor cell. The person of ordinary skill in the art would understand this from the wording of the claims, which entail two steps, preparing donor cells and contacting target cells with donor cells in such a way that an oligonucleotide or peptide is delivered from the donor cell to the target cell via gap junctions.

Claims 1, 3, 4, 10-12, 14, 19, 20, 21, and 23 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Burt et al. (American J. of Physiology: Cell Physiology, 2001 Vol. 280, pp. C500-8).

Burt et al. examined the Cx43:Cx40 expression ratio in A7r5 cell line clones and correlated the ratios with electrical and dye coupling. In an attempt to reduce the levels of Cx43 thereby altering the Cx43:Cx40 ratio, Burt et al. express Cx43 antisense RNA in cell lines. Burt et al. neither teaches nor suggests a method wherein an oligonucleotide or plasmid is first introduced into a donor cell and then, second, the donor cell is used to introduce the oligonucleotide, or a plasmid expressing an oligonucleotide, or a peptide product thereof, to the target cell via gap junctions. In fact, by purposefully reducing the levels of Cx43, which forms gap junctions, Burt et al. would inhibit this second step from occurring via Cx43 gap junctions.

Further, in Burt, as in Li and Frendo, there is only one population of cells, the cells into which the oligonucleotides are introduced. In the claimed methods, there are two populations of cells, the donor cells, into which the oligonucleotide or plasmid is introduced in step a), and the target cells, into which the oligonucleotide or the plasmid is not introduced in step a), but rather which receives the oligonucleotide only as a consequence of being contacted with the donor cell. The person of ordinary skill in the art would understand this from the wording of the claims, which entail two steps, preparing donor cells and contacting target cells with donor cells in such a way that an oligonucleotide or peptide is delivered from the donor cell to the target cell via gap junctions.

In sum, the Applicants respectfully submit that the art cited by the Examiner does not disclose the claimed method as presented in this amendment comprising, first, introducing an oligonucleotide or a plasmid into a donor cell in vitro; and second, contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide, the plasmid expressing the oligonucleotide, or a peptide product thereof, is delivered into the target cell from the donor cell by traversing the gap junction. The cited art does not disclose such a method and therefore does not disclose each and every element of the claims. Therefore, the Applicants respectfully submit that the claims are not anticipated under section 102 by the art cited.

Rejection Under 35 U.S.C. § 103

Claims 1-14 and 19-23 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over either Frendo et al., Li et al, or Burt et al. in view of Hammond et al. (Nature Reviews, 2001 Vol. 2, pp. 110-9).

Frendo et al. examined the involvement of Cx43 in trophoblast cell fusion by introducing Cx43 antisense RNA into human villous cytotrophoblasts. Frendo et al. introduced the Cx43 antisense RNA into human villous cytotrophoblasts in order to reduce the expression of Cx43. Frendo et al. neither teaches nor suggests a method wherein an oligonucleotide, or plasmid, is introduced into a donor cell and then the donor cell is used to introduce the oligonucleotide, or a plasmid expressing an oligonucleotide, or a peptide product thereof, to the target cell via gap junctions. In fact, by purposefully reducing the levels of Cx43, which forms gap junctions, Frendo et al. teaches away from the present invention, which utilizes the formation of gap junctions between the donor and target cell.

Li et al. studied Cx43 hemichannels, which are Cx43 assemblies in the plasma membrane of a cell that have not formed a gap junction with another cell. Li et al. transfected a Cx43 antisense expression vector into Novikoff cells in order to reduce the levels of Cx43. Li et al. neither teaches nor suggests a method wherein an oligonucleotide or plasmid is introduced into a donor cell, and then the donor cell is used to introduce the oligonucleotide, or a plasmid expressing an oligonucleotide, or a peptide product thereof, to the target cell via gap junctions. In fact, by purposefully reducing the levels of Cx43, which forms gap junctions, Li et al. teaches away from the present invention, which utilizes the formation of gap junctions between the donor and target cell.

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Hammond et al. reviews the history of the discovery of post translational gene silencing and RNAi and reviews the knowledge, models, and uses for these processes. Hammond et al. do not teach or suggest a method wherein an oligonucleotide or plasmid is introduced into a donor cell and then the donor cell is used to introduce the oligonucleotide, or a plasmid expressing an oligonucleotide, or a peptide product thereof, to the target cell via gap junctions. Thus, Hammond does not provide the element missing from the other cited prior art, namely, the use of two populations of cells, the donor cells, into which a recited nucleic acid is initially delivered (the donor cells), and the target cells, which receive the recited nucleic acid only from the donor cells.

Thus, none of the cited prior art teaches, suggests, or would have motivated the person of ordinary skill in the art to introduce into a donor cell an oligonucleotide or plasmid expressing an oligonucleotide, or RNA or a plasmid transcribable into RNA, or DNA or a plasmid coding for the DNA, and then contact a target cell with the donor cell, the target cell, as recited by the claims, not having had introduced into it the material of the first step. That is, the cited prior art does not teach, suggest, or motivate the use of two distinct populations of cells, the donor cells, into which the recited nucleic acid is introduced, and the target cells, which only receive the nucleic acid as a consequence of being contacted by the target under conditions that permit formation of a gap junction channel between the donor cell and the target cell, as the claims recite.

As noted above, this is the primary difference between the cited prior art and the claimed methods. None of the cited prior art would have motivated the person of ordinary skill in the art to change the prior art methods from using a single population of cells to using two populations of cells because only a single population of cells was needed to study the phenomena addressed in the cited prior art (such as the properties of gap junctional hemichannels in cultured cell membranes (Li et al.), the consequence of altering the Cx43:Cx40 expression ratio (Burt et al.), and the involvement of Cx43 in human trophoblast cell fusion and differentiation (Frendo et al.)). It is only with the impermissible use of hindsight that it could be argued that the cited prior art would have motivated the person of ordinary skill in the art to employ two cell populations instead of the single population used in the prior art.

In fact, Frendo et al., Li et al, and Burt et al. teach away from the present invention because each teaches the introduction of Cx43 antisense RNA in order to reduce the levels of Cx43, which forms gap junctions necessary for the second step of the claimed

invention. Therefore, Applicants respectfully submit that the pending claims are not rendered obvious under 35 U.S.C. § 103 by the disclosure of Frendo et al., Li et al, or Burt et al. in view of Hammond et al.

In sum, Applicants respectfully submit that the art cited by the Examiner does not teach or suggest the claimed methods. All of the art cited merely introduces the oligonucleotide directly into the target cells. In contrast, the present invention comprises, first, introducing the oligonucleotide or the plasmid into a donor cell; and second, contacting the target cell with the donor cell, whereby the oligonucleotide, the plasmid expressing the oligonucleotide, or a peptide product thereof, is delivered into the target cell from the donor cell via a gap junction.

Applicants believe that the present application is in condition for allowance, and respectfully request that the Office pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

The Office is authorized to charge any additional fees that may be necessary for consideration of this paper to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

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